UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/749,522	01/02/2004	Beka Solomon	SOLOMON=2B.2	9533

1444 7590 08/18/2006

BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
BALLARD, KIMBERLY A	
ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 08/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/749,522	SOLOMON ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 25-34* is/are pending in the application.

4a) Of the above claim(s) *1-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-11 and 25-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/9/04, 3/25/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

Applicant's response and amendment to claims filed 13 June 2006 has been entered. Claim 7 has been amended, claims 12-24 have been cancelled, and new claims 25-34 have been added. Claims 1-11 and 25-34 are pending.

Election/Restrictions

Applicant's election with traverse of Group II, claims 7-11 directed to a pharmaceutical composition, and species election of SEQ ID NO: 7, in the reply filed on 13 June 2006 is acknowledged. The traversal is on the ground(s) that a similar restriction requirement between composition and method of use was withdrawn in parent, grandparent, and great-grandparent applications. This is not found persuasive because each application is prosecuted on its own merits. Additionally, Applicant has not sufficiently established that there would not be an undue burden upon the Office to search and examine the composition of Group II and the method of using of Group I together. As discussed at page 4 of the restriction requirement (02/13/2006), the inventions of Groups II and I are related as product and process of using, but are distinct because the pharmaceutical composition of Group II could be used instead in a method of diagnosing Alzheimer's disease, and the method as claimed could be practiced with another anti-β-amyloid antibody that binds to a different epitope of β-amyloid. Accordingly, there would be a search burden upon the Examiner to examine the inventions together. Applicant is reminded that where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn

process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04.

The requirement is still deemed proper and is therefore made FINAL.

In regard to the species election, the Examiner regrets that SEQ ID NO: 1 was not included as a choice for election. Upon further consideration, the species election requirement is hereby *withdrawn.*

Claims 1-6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 13 June 2006.

Claims **7-11** and **25-34** are under examination in the current office action.

Applicant's response submitted 13 June 2006 regarding the Office action of 02 July 2003 in parent application 10/162,889 is noted, however, again Applicant is reminded that each application is prosecuted on its own merits. The declarations of Drs. Beka Solomon and Birgit Hutter-Paier are also noted, and have been entered into the file record.

Information Disclosure Statement

Signed and initialed copies of the IDS paper submitted 09 June 2004 and 25 march 2005 are enclosed in this action. It is noted that some references have been

lined through because they are duplicated or do not list source/date information. The printer has been instructed to not print these references.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7-11 and 25-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Solomon et al. (*Proc Natl Acad Sci USA*, April 1997; **94**: 4109-4112 as listed on Applicant's IDS) and Hanan & Solomon (*Amyloid: Int J Exp Clin Invest*, 1996; **3**:130-133, listed on IDS), both as evidenced by Frenkel et al. (*J Neuroimmunol*, August 1998; **88**: 85-90, listed on IDS), and both in view of US Patent No. 5,846,533 to Prusiner et al., issued 8 December 1998, filed 13 September 1996 (listed on IDS), and Pasqualini (*Mol Psychiatry*, 1996; 1: 423, listed on IDS).

The claims are drawn to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as an active ingredient, a filamentous bacteriophage which displays an antibody or binding fragment thereof, wherein said antibody binds to an epitope of β-amyloid so as to inhibit aggregation and/or cause disaggregation of β-amyloid in a subject (claims 7-11). The claims are also directed to a composition comprising a carrier and said bacteriophage displaying said antibody or epitope binding fragment (claims 25-29). The claims are further drawn to a filamentous bacteriophage that displays an antibody or epitope binding fragment thereof as described above (claims 30-34). Additional claim limitations include: wherein said epitope of β-amyloid comprises SEQ ID NO: 1 (claims 8, 26, and 31), wherein said antibody or binding fragment is displayed on said bacteriophage via coat glycoprotein VIII (claims 9, 27, and 32), wherein said epitope is contained in a peptide selected from the group consisting of SEQ ID NOS: 7, 8, 21 and 22 (claims 10, 28, and 33), and wherein said β-amyloid is selected from the group consisting of Aβ39, Aβ40, Aβ41, Aβ42, and Aβ43 (claims 11, 29, and 34).

The teachings of Solomon et al. (1997) and Hanan & Solomon (1996) are cumulative. Both references teach the inhibition and disaggregation of β-amyloid peptide by monoclonal antibodies. The monoclonal antibodies found to be significantly effective in interfering with the aggregation of β-amyloid *in vitro* are 6C6 and 10D5, both of which recognize an epitope within Aβ1-16 (see Figure 1 of each reference). Solomon (1997) also demonstrates that the 6C6 mAb (monoclonal antibody) was effective at inhibiting the neurotoxic effects of fibrillar β-amyloid on PC12 cells in culture (see Figure 4, p. 4111). For these experiments, the antibodies were added in a composition comprising phosphate-buffered saline (PBS) (see p. 4110, 1st paragraph), thus meeting a recited limitation of a pharmaceutically acceptable carrier or simply, a carrier. Although the specific anti-aggregating epitope that these antibodies recognize is not specifically recited by the authors, subsequent work from this group established that the N-terminal EFRH sequence, which is the instantly claimed SEQ ID NO: 1, is residues 3-6 of β-amyloid and represents the sequential epitope of mAbs 6C6 and 10D5 (see Frenkel et al., 1998), thus meeting a recited limitation of instant claims 8, 26, and 31. The EFRH sequence is also contained within each of the amino acid sequences of SEQ ID NOS: 7, 8, 21, and 22, thus meeting another recited limitation of instant claims 10, 28, and 33. Solomon et al. (1997) notes that Alzheimer's disease-associated plaques are predominantly comprised of a 40- to 42-mer β-amyloid peptide (see p. 4109, 1st paragraph), thus meeting a recited limitation of claims 11, 29, and 34. Solomon et al. (1997) thus suggests that high-affinity, site-directed mAbs (or compounds that may mimic their biological activities as genetically engineered small antibodies or peptide

mimetics), which trigger reversal of the pathological aggregation of β-amyloid to its nontoxic components, may be used in the development of therapeutic active molecules for the treatment of such diseases as Alzheimer's disease and prion diseases (see p. 4112). And Hanan & Solomon (1996) add that through advances in antibody engineering techniques and the development of suitable delivery systems, functional small antibody fragments may serve as new therapeutic approaches for the treatment of Alzheimer's disease, as well as other human amyloid diseases (see p. 132, final paragraph).

However, Hanan & Solomon do not elaborate as to what such suitable delivery systems of the therapeutic antibody fragments may be. Neither Solomon et al. (1997) nor Hanan & Solomon (1996) teach compositions comprising filamentous bacteriophage which displays an antibody or epitope binding fragment thereof.

Prusiner et al. teach methodologies for producing a variety of different prion protein antibodies for use in neutralization or purification of prion proteins or for therapeutics (see column 4, lines 61-67). For this purpose, Prusiner et al. teach genetically engineered phages which express a specific binding protein of an antibody on their surfaces (see column 5, lines 3-5). Additionally, Prusiner et al. disclose that the antibody can be bound to a detectable label and injected into an animal to assay *in vivo* for the presence of a particular type of native prion protein (see column 11, lines 28-30), or such antibodies can be used to treat a mammal (see column 21, lines 25-26). Prusiner et al. teach that antigen-based selection from antibody libraries expressed on the surface of M13 filamentous phage offers a new approach to the generation of monoclonal antibodies and possesses a number of advantages relative to hybridoma

technologies (see column 15, lines 61-65). The desired peptide, such as an antibody or Fab or Fv antibody fragment (see column 23, lines 31-32), displayed on the surface of a filamentous phage (e.g., M13, f1, fd, and equivalent filamentous phages) is anchored via a membrane anchor domain found in the coat proteins encoded by gene III or gene VIII (i.e., cpIII or cpVIII coat proteins) (see column 24, line 38 through column 25, line 4, and column 26, lines 35-41), thus meeting a recited limitation of instant claims 9, 27, and 32.

Finally, Pasqualini teaches the targeting of specific tissues, such as brain, with phage peptide libraries (see entire article). Pasqualini teaches a method of selecting for phage molecules capable of homing into target tissues *in vivo*, and suggests that this method may provide a new means for selective targeting of therapies. For example, Pasqualini suggest that a brain-selective phage motif can be used to direct particles (such as therapeutic or diagnostic peptides) into the brain capillaries.

It would have been obvious to one of skill in the art at the time the invention was made to modify the monoclonal antibodies taught by Solomon et al. (1997) and Hanan & Solomon et al. (1996) by displaying the Aβ anti-aggregating epitope of the antibodies, which comprises residues 3-6 of Aβ (EFRH), on the surface of a filamentous bacteriophage, as taught by Prusiner et al., either alone or as a composition comprising a pharmaceutically acceptable carrier. Specifically, the artisan would be motivated to make such modifications because Solomon et al. and Hanan & Solomon teach that this region (EFRH) comprises an epitope particularly important for inhibiting the aggregating and neurotoxic properties of the Aβ peptide, and thus small antibodies or antibody

binding fragments to this region would be useful for therapeutic applications in the treatment of diseases associated with amyloid aggregation, such as Alzheimer's disease. And Prusiner teaches that combinatorial antibody library technology (i.e., antibodies displayed on filamentous phages) is advantageous over traditional hybridoma methodologies for the generation of monoclonal antibodies. The skilled artisan would likewise be motivated to express such Aβ antibody or epitope binding fragments thereof on filamentous phages because Pasqualini teaches that such technology may be used for selective tissue targeting, such as the targeting of therapeutic molecules to the brain. Accordingly, the artisan would be motivated to produce a filamentous phage displaying an antibody or antigen binding fragment directed against the anti-aggregating epitope of β-amyloid peptide, and pharmaceutical compositions comprising same, for potential use in therapeutic applications. Such combination would be met with an expectation of success by the artisan based upon the well-established methodology of expressing antibodies or antibody binding fragments on the surface of bacteriophages, as in the construction of phage display libraries (see for example, Prusiner et al., column 21, lines 58-67). Thus, the combined references render the claimed invention obvious to the artisan at the time the invention was made.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kimberly Ballard, Ph.D.
Art Unit 1649
August 11, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER